Modern Concepts of Cardiovascular Disease

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CARDIOVASCULAR MANIFESTATIONS IN SOME OF THE COMMON INFECTIOUS DISEASES*

Involvement of the cardiovascular system occurs in many of the common infectious diseases. Although they are usually not detectable clinically, anatomic and functional changes in cardiac tissue appear more frequently than has been recognized. It must be stressed, however, that they are rare in most of the infections seen in the daily practice of medicine in this country. The development of more precise methods of study and more careful search for cardiovascular abnormalities have led to the discovery that even mild infectious diseases may be complicated by phenomena which, if they do not threaten life immediately, may produce trouble in the future. It is the purpose of this paper to review briefly the cardiovascular changes which have been noted in some of the infectious diseases which are seen frequently in the general practice of medicine and pediatrics, to point out the nature of the processes, their incidence, wherever this is possible, and their immediate and late significance.

BACTERIAL DISEASES

Beta-hemolytic Streptococcus Infections: The cardiovascular involvement most often detected following infection with the beta-hemolytic *Streptococcus* is acute rheumatic carditis. If rigid criteria are used for diagnosis, the incidence of rheumatic fever following a proved attack of streptococcic pharyngitis is on the average 2 to 3 per cent. In this group the myocarditis and valvulitis, as well as the pericarditis which occurs less frequently, are frequently clinically apparent because arrythmias, increase in heart size, varying degrees of heart failure, changing murmurs over the apex and base of the heart, and friction rubs can be detected from 10 days to 6 weeks after the initiation of the pharyngeal infection. It is well known that severe rheumatic involvement not infrequently produces a pancarditis and that in some instances the process may be so severe that death occurs despite the application of the best available therapy. Anatomic studies in such cases usually demonstrate the presence of Aschoff bodies and changes in the valves and pericardium characteristic of acute rheumatic carditis. It has recently been suggested that severe carditis and death following streptococcal pharyngitis may be due to a severe and extensive myocarditis in which the type of cellular reaction is very different from that of rheumatic fever.

Although it is impossible on clinical grounds alone to define any features which distinguish the myocarditis of rheumatic fever from that which occurs after scarlet fever, it has been thought for many years by some that the "scarlet fever heart" is different from rheumatic carditis, although this contention has never been proved. A recent study of this problem in 27 fatal cases of untreated scarlatina revealed myocarditis in 70 per cent; clinically the cardiac complication was recognized in only 10 per cent. In the absence of streptococcal pneumonia, pleurisy, pericarditis, or acute glomerulonephritis, the hearts of these patients were noted to contain subendothelial and perivascular infiltrates of small round cells and focal infiltrates of similar cells not characteristically located in the myocardium. In more than half the cases, especially in the severe ones, the focal collections of cells were associated with small areas of acute hyaline or granular necrosis of muscle. This type of lesion has also been described in the hearts of patients who have died of streptococcal bacteremia. Sudden death, conduction disturbances, or arrythmia occur in some cases. The relationship of this kind of myocarditis to that which is present in rheumatic fever still remains to be clarified.

Electrocardiographic studies in streptococcic pharyngitis and scarlet fever reveal a greater incidence of abnormality than can be suspected on the basis of physical examination alone. In several studies, from 7 to 15 per cent of patients have had abnormal electrocardiograms. Although the incidence has been recorded as being much higher in some investigations, some of the changes must be

*From the Haynes and Evans Memorials of the Massachusetts Memorial Hospitals and the Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

disregarded because tracings were made at a time when fever and tachycardia were present. The significant abnormality observed most often has been prolongation of the P-R and Q-Tc intervals. It has been suggested that such changes are supracardiac in origin and have no significance in relation to the presence of myocarditis; this suggestion is difficult to accept because the electrocardiographic abnormality appears very frequently only after defervescence has taken place and recovery from the acute infection is well on the way. Controversy has arisen regarding the relation of such altered conduction to acute rheumatic carditis; this question will probably be settled only by long term follow-up studies of persons who have had electrocardiographic changes alone, without any clinical abnormalities, after an authenticated attack of streptococcal pharyngitis.

Staphylococcal Infections: Staphylococcus aureus is one of the bacteria which frequently produces human infection. This organism merits special attention because so many strains are presently resistant to most of the available antibiotic agents. During the course of staphylococcal bacteremia, which may be initiated by as minor a lesion as a "pimple" if it is squeezed or injudiciously incised, the organisms may become implanted on one of the heart valves and produce acute endocarditis. In 60 per cent of patients, the involved valve is normal prior to infection; the aortic valve is the one most frequently attacked. In the early stages of this type of endocarditis there may be very few symptoms except for mild fever, and the disease may progress without attracting attention until embolic phenomena appear. In addition to ulcerative lesions of valves, acute myocarditis and multiple abscesses of cardiac muscle may be present in fatal cases.

Diphtheria: It has been recognized for many years that severe myocarditis is not an uncommon complication of diphtheria and that this lesion is responsible for most of the deaths in this disease. Myocarditis is recognized clinically in about 10 per cent of cases. Among the abnormalities which can be detected by physical examination are softening of the heart sounds, extra-systoles, gallop rhythm, auricular fibrillation, ventricular tachycardia, heart block, and cardiac decompensation. Congestive failure occurring during diphtheria is related mainly to inadequacy of the right side of the heart. Pain in the right upper quadrant of the abdomen together with rapidly developing hepatomegaly are often the first manifestations of heart failure, while basal pulmonary rales are detectable much less frequently and may not appear until relatively late. Among the electrocardiographic abnormalities, which are frequently demonstrable, are prolonged AV conduction, bundle branch block, complete and incomplete block, auricular flutter or fibrillation, and in practically all fatal cases ventricular fibrillation as a terminal event.

Anatomic studies of the heart in fatal diphtheria reveals dilatation of the chambers, flaccidity, pallor and streaking of the myocardium, noted singly or in various combinations. In patients who have had myocarditis for 3 weeks or longer, varying degrees of scarring may be apparent. Microscopically, scattered foci of hyaline and granular degeneration of muscle fibers, infiltration with histiocytes, lymphocytes and plasma cells and myolosis, disintegration or "dropping out" of degenerated muscle fibers as well as fat phaneuresis of myocardial muscle are present.

Serial electrocardiographic studies of patients with diphtheria indicate that myocarditis occurs with considerably greater frequency than is suspected on the basis of clinical findings. The reported incidence of abnormal tracings varies between 23 and 84 per cent. The commonest findings are abnormal T waves and ST-T segments. Although prolonged AV conduction occurs, it is not, as has been suggested, the most common defect.

If the electrocardiographic abnormalities are graded from 1 to 4 on the basis of severity, group 4 including instances of bundle branch and incomplete or complete heart block, ventricular tachycardia and auricular fibrillation, the mortality rate has been found in one investigation to be 5 per cent in Grade 1 and 89 per cent in Grade 4. Clinical-anatomical correlations in patients studied electrocardiographically point out that the histologic changes are frequently more widespread and severe than would be expected from the electrical tracing.

There is very good evidence that recovery from an episode of diphtheritic myocarditis is not associated in many instances with a return of the heart to either an anatomically or functionally normal state. If cardiac disease has been present for longer than 3 weeks, there is usually a varying degree of myocardial fibrosis; this is often more extensive than can be predicted on the basis of electrocardiographic changes. Patients studied months to years after recovery from diphtheritic myocarditis have been found to have persistently abnormal electrocardiograms, cardiac enlargement, abnormal heart sounds, and varying degree of heart block. It is obvious that the heart disease which occurs during diphtheria is not benign, even if recovery takes place, and that it may produce trouble later in life by depleting the reserve which is important at an older age when hypertension or coronary artery disease may occur.

Rarely, a patient with diphtheria who appears to be convalescing normally suddenly develops severe shock and dies despite all efforts to reverse the severe hypotension. In some instances autopsy reveals an unrecognized myocarditis of severe degree; in most, the heart is apparently normal and the cause for the shock state cannot be discovered.

Pertussis: Despite the severe degree of bronchitis and the extensive atelectasis and pneumonia which may occur frequently in whooping cough, cardiac abnormalities practically never appear. In a rare fatal case dilatation of the chambers of the right heart is detectable. There is a dearth of information concerning electrocardiographic changes in pertussis. A recent serial electrocardiographic study in a group of children (most of them under 2 years of age) has revealed the almost universal presence of changes consistent with right heart strain during the period of most severe paroxysmal coughing. In every instance, recovery from infection with decrease of cough has been associated with a return of the electrocardiogram to normal.

VIRAL DISEASES

Measles: Measles is usually not a fatal disease unless some complication such as secondary bacterial infection or encephalitis occurs. For this reason reports of anatomical changes in the myocardia of patients who have succumbed to rubeola are very difficult to evaluate in most instances, since it is impossible to determine whether the abnormalities have been produced by measles per se or whether they merely represent a myocarditis which is causally related to one of the complications. Taking this into consideration, it appears that anatomic changes in the heart in uncomplicated rubeola are probably very rare. Clinical manifestations of myocarditis have been recorded in several instances. Bundle branch block, asymptomatic heart block, and ventricular tachycardia have been noted. One case of heart block persisting for 4 years following an attack of measles has been described. There is a record of a 2-year old child who developed heart block following rubeola and who died two years later during a Stokes-Adams attack.

A current study by serial electrocardiography of 106 patients with measles has revealed significant changes in 20; 12 had major T wave abnormalities; in 7, AV conduction was prolonged; one exhibited auricular premature beats. Only 3 of the 12 cases with T wave changes were febrile; while none of those with an increased P-R interval had an elevated temperature during the period when the electrocardiogram was abnormal. T wave changes were observed as early as 3 days and as late as 19 days after the onset of the rash; two-thirds appeared during the first 8 days. Prolonged AV conduction occurred from the second to the twentieth day of infection. The electrocardiographic abnormality was always of brief duration and usually disappeared in a few days. The development of changes in the electrocardiogram was not found to be related to the severity of the measles. In no case were there any symptoms or signs consistent with the presence of a myocarditis. In another study it was claimed that prolonged P-R intervals appeared in 30 per cent. This seems to be extraordinarily high and is not confirmed by the investigation cited above.

Mumps: Anatomic evidence of myocarditis has been demonstrated rarely in cases of mumps which have come to necropsy. Although clinical evidence of involvement of the cardiovascular system during the course of epidemic parotitis is also very rare, heart block of varying degree has been observed. In one patient, complete heart block which appeared during the acute phase of the infection persisted for 3 months after recovery. In an electrocardiographic study of this disease, significant changes were observed in 15 per cent. Prolonged A-V conduction was found in 1.9 per cent. The other abnormalities consisted of inversion of QRS, elevation or depression of S-T segments, and changes in direction and size of T waves. The electrocardiographic abnormalities appeared between the fifth and tenth day of illness and were transitory, disappearing in 2 to 35 days; in most instances the curves were normal in 4 to 8 days. Precordial pain, either alone or with dyspnea and palpitation, was noted in a few patients. These data suggest that some degree of myocarditis may occur occasionally in mumps; the significance of these findings is difficult to evaluate, however, until further follow-up studies and clinical-anatomical correlations have been made.

Chicken Pox: Fatal cases of chicken pox are rare and usually are associated with a complication of the disease such as primary viral or secondary bacterial pneumonia or encephalitis or both. Although focal interstitial inflammatory lesions of the myocardium have been noted in patients who have succumbed to varicella, the relation of these to the primary viral disease is impossible to establish with certainty because the cardiac damage may have been due to the complication. It has been suggested that electrocardiographic abnormalities also may appear during the course of chicken pox; the significance and true incidence of such changes has not yet been determined.

Poliomyelitis: The cardiovascular abnormalities which occur during the acute phase of poliomyelitis include hypertension, anatomical changes in heart muscle, electrocardiographic abnormalities, pulmonary edema, and shock.

Hypertension is a fairly frequent accompaniment of the types of poliomyelitis in which there is respiratory difficulty. In most instances it can be shown to be associated with hypoventilation and to be related to hypoxia. Such elevation of the blood pressure is practically always eliminated by the application of measures which increase oxygenation — the administration of oxygen, suction and gravity drainage, the use of tank or phrenic respirators, or tracheotomy. Uncommonly a much more important type of hypertension appears during poliomyelitis particularly when bulbar or phrenic — intercostal paralysis are

present. This elevation of the blood pressure may appear suddenly or progressively, may reach high levels, cannot be associated with hypoventilation, and may persist long after the acute phase of the infection is over. This form of hypertension has been related to disease of the hypothalamus. The writer has recently studied one patient whose blood pressure was 260/160 following an episode of paralytic poliomyelitis from which he was recovering. The eye-grounds revealed marked spasm of the arterioles, arterio-venous nicking, hemorrhages, exudates, and papilledema. As far as could be ascertained, hypertension was not present prior to the onset of the poliomyelitis. The patient had had several crises associated with hypertensive encephalopathy before therapy with hypotensive drugs was undertaken. Investigation for renal or vascular causes for the elevated blood pressure and studies for the presence of a pheochromocytoma were unrevealing. The problem of hypertension in poliomyelitis, particularly of the type that persists, merits serious attention especially in relation to the mechanisms involved because many of its features are very similar to those of so-called essential hypertension, even the "malignant" variety.

Anatomical changes that have been interpreted as myocarditis have been reported in from 40 to 90 per cent of patients dying from poliomyelitis. The commonest lesion in the heart muscle consists of focal interstitial collections of lymphocytes. Some doubt has been raised concerning the significance of such findings since they have also been noted in the hearts of patients who have died of other diseases, some of which have not been infectious. It has been suggested that this type of myocardial infiltration is due to hypoxia since it is frequently present when death has been preceded by an asphyxial state of variable duration. There is another type of myocarditis in poliomyelitis which is much less common than the one just described. It is characterized by necrosis of muscle cells and a neutrophilic infiltrate and appears to be causally related to the virus infection because clinical manifestations of cardiac disease may be present for some time prior to death. The causative agent of poliomyelitis has been isolated from the hearts of patients at necropsy.

Electrocardiographic abnormalities have been observed in the acute phase of poliomyelitis in a fairly large number of patients with this disease. The reported incidence of such changes unrelated to fever and tachycardia has varied between 5 and 25 per cent. Prolonged P-R and QTc intervals, widening of the QRS complex, depression of the ST segment and T wave changes have been noted. Electrocardiographic patterns consistent with either anterior or posterior wall infarction have been seen during the course of infantile paralysis by the writer. In most cases, there are no detectable clinical signs of cardiac dysfunction at the time when the electrocardiographic records are abnormal; in some, extra-systoles, tachycardia, auricular fibrillation, pain in the chest, changes in heart sounds, and pulmonary edema may be present.

Pulmonary edema occurs occasionally, usually as a terminal event, in poliomyelitis with bulbar involvement or paralysis of the muscles of respiration. In a few cases the presence of an associated severe myocarditis can be demonstrated. In others the heart is normal both clinically and anatomically. In the latter the edema of the lungs is probably produced by the same "central" mechanisms which are responsible for its development after cerebral hemorrhage and with severe meningitis or sudden increase in intracranial pressure as may be seen with brain abscess or with some tumors.

In practically all cases of fatal bulbar poliomyelitis the terminal event is one of severe hypotension and the appearance of the classical manifestations of severe shock. Involvement of the center for vasomotor control in the medulla by the virus has been thought to be responsible for this phenomenon. It is a completely unpreventable and untreatable complication of poliomyelitis, and death always ensues despite the occasional transient elevation of blood pressure which follows the use of potent vasoconstricting agents.

Influenza: Circulatory failure was observed with great frequency during and after the 1918 pandemic of influenza. Cardiac dilatation, sudden death during convalescence, bradycardia, extrasystoles, partial and complete heart block have been noted by various students of this disease. Electrocardiographic studies have revealed sinus-nodal block, loss of various complexes, bizarre ventricular complexes, and T wave changes. Among the signs and symptoms in influenza that suggest the presence of cardiac involvement are weakness, dyspnea, palpitation, anginoid pain, extreme malaise, Stokes-Adams attacks, and sudden death. These symptoms are said by some writers to be as frequent after influenza as they are in mitral stenosis. Cardiac abnormalities have been observed in sporadic as well as epidemic cases of this infection and are commonest during convalescence. Although many investigators think that heart disease occurs fairly often in epidemic influenza, others think that this complication is rather infrequent.

Anatomic studies of the hearts of patients who have died of influenza virus infection reveal that myocarditis may occur. Necrosis of cardiac muscle and infiltration of the myocardium with lymphocytes, plasma cells, large mononuclears, eosinophiles, and mast cells have been described. It has been postulated that the myocardial lesions are the result of infection by the influenza virus and not non-specific changes associated with disease of the respiratory tract.

Infectious Mononucleosis: Cardiac abnormalities have been observed during the course of infectious mononucleosis on rare occasions. Electrocardiographic changes suggestive of pericarditis, T wave abnormalities, and ventricular extra-systoles have been described. Since death in this infection is very rare and there are, therefore, very few autopsied cases, there is very little information concerning anatomical changes in the heart. Infiltration of the myocardium by abnormal "lymphocytes" of the same type as are characteristically present in the peripheral blood has been reported. Glandular fever is a very common disease which, as both clinical and laboratory studies suggest, may produce extensive and severe involvement of many tissues and organs. This disease, therefore, merits more intensive and serious attention from the standpoint of detection of cardiovascular abnormalities than it has received up to the present.

Primary "Atypical" Virus Pneumonia: Electrocardiographic abnormalities may appear during the course of "atypical virus pneumonia." Increased AV conduction time, abnormal T waves, and changes consistent with acute pericarditis have been recorded. One investigator has reported an incidence of 11 per cent abnormal electrocardiographic tracings in 100 persons with this type of pneumonitis. In another study of 321 patients 3.7 per cent had abnormal electrocardiograms. In some instances the tracings have been found not to return to normal for several months. Gallop rhythm and pericardial friction rub have been noted in rare cases.

SUMMARY AND DISCUSSION

Cardiovascular involvement of varying degree occurs in most of the common infectious diseases. Anatomical and electrocardiographic studies as well as clinical observation suggest that in some of the infections the cardiac damage may be severe and that the prognosis for complete recovery may be uncertain. It must be stressed, however, that most of the evidence for the presence of heart involvement during an infectious disease has been obtained from laboratory study and that clinical support is for the most part lacking with the exception of such diseases as diphtheria and rheumatic fever. This necessitates a careful evaluation of the laboratory data in terms of the primary disease and its complications. There is a great need for more intensive study of this phase of the problem of infection, especially in the field of clinical-anatomical-electrocardiographic correlation.

Since involvement of the cardiovascular system may occur in the infections which affect practically all people, it becomes necessary to determine what impact this type of cardiac disease may have on the patient later in life. It is very probably wrong to assume that, because there are no clinical manifestations and recovery seems to be complete, the cardiac process is necessarily benign. That this is not so is well pointed out by the myocarditis of diphtheria and rheumatic fever in which important residual damage often becomes a threat long after the primary illness has disappeared. It is immediately obvious, therefore, that the only method by which the true significance of cardiac involvement in some of the common infectious diseases can be determined and this type of heart disease placed in its proper perspective in the field of cardiovascular dysfunction is a careful follow-up study, which should encompass many years rather than just a few weeks or months. This type of research does not require any special equipment or laboratory. It can and will probably be best carried on by the practicing physician because he is in the best position to see patients when they are in the acute stages of the common infectious diseases and to arrange for and carry out the long-term study by means of which important contributions to our knowledge will be made.

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The opinions and conclusions expressed herein are those of the author and do not necessarily represent the official views of the Scientific Council of the American Heart Association.

SECOND WORLD CONGRESS OF CARDIOLOGY AND THE 27TH ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION, INC.

September 12-17 Washington, D.C.

All those planning to attend the Congress are urged to *submit their applications at the earliest possible date. Any physician may attend the Congress by filling out and sending in the application blank and paying the required registration fee.* Detailed information concerning the Congress is available from the Secretary-General, L. W. Gorham, M.D., Second World Congress of Cardiology, % American Heart Association at 44 East 23rd Street, New York 10, N. Y.

MEMBERSHIP

A registration fee of $25.00 has been established for the combined World Congress and Scientific Sessions. Although registration fees have not been charged professional members of the American Heart Association attending the Annual Scientific Sessions in previous years, the expense of the enlarged and integrated sessions of the forthcoming Congress and the many events associated with it require that a fee be charged this year. The $25.00 fee entitles members to attend all scientific sessions, the opening reception, formal banquet and other social events, exhibits and special sightseeing tours in Washington and its environs. Also included are the printed programs, Congressional badge and other items.

Associate membership (wives and family) has been arranged at a cost of $15.00. It will include all privileges mentioned above except the printed program. *A schedule of reduced fees has been provided for limited attendance by physicians and for attendance by such groups as medical students, interns, and nurses.*

SCHEDULE

A tentative schedule of the Congress follows:

Saturday, Sept. 11, 5:00 to 10:00 p.m.: Registration, Mayflower Hotel

Sunday, Sept. 12:

9:00 a.m. to 10:00 p.m.: Registration, Mayflower Hotel
10:30 a.m.: Opening ceremonies at Constitution Hall
8:30 p.m.: Reception for Congress Members, Pan American Building

Monday, Sept. 13 through Friday, Sept. 17: Scientific Sessions at National Guard Armory. Sessions will consist of lectures by special invitation, symposia and panel discussions in a large auditorium and presentation of original scientific papers in each of four smaller rooms.

Morning sessions will be held every day from 9:00 a.m. to 12:30 p.m.
Afternoon sessions will be held every day except Wednesday, Sept. 15 and Friday, Sept. 17, from 2:00 p.m. to 5:30 p.m.

Monday, Sept. 13, 8:30 to 10:30 p.m.: Visit to National Gallery of Art, for Congress Members only.

Tuesday, Sept. 14, 8:00 p.m.: Formal banquet for Congress Members, to be held simultaneously at Mayflower and Statler Hotels.

Wednesday, Sept. 15, 2:30 p.m. to 5:30 p.m.: Medical sightseeing tours.

Thursday, Sept. 16, 8:30 p.m.: National Symphony Orchestra Concert.

Friday, Sept. 17, 2:30 to 5:30 p.m.: Medical sightseeing tours.

EXHIBITS

Scientific and industrial exhibits have been planned for the Congress, as well as a motion picture program of professional and scientific films on cardiovascular subjects.